09567863

drug-resistant tumors to vinblastine or doxorubicin in an ascitic or solid tumor model, resp. No alteration in the plasma pharmacokinetic profile of doxorubicin by CL 329,753 has been found. Furthermore, the compd. had 70-fold less calcium channel antagonistic activity compared with verapamil.

=>

09567863

s p glycoprotein and sensit? and treatment and chemother?
L2 1277 P GLYCOPROTEIN AND SENSIT? AND TREATMENT AND CHEMOTHER?

=> s l2 and resisitance
L3 1 L2 AND RESISITANCE

=> s l2 and resistance
L4 1199 L2 AND RESISTANCE

=> s l4 chemosensiti?
MISSING OPERATOR L4 CHEMOSENSIT
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l4 and chemosensit?
L5 266 L4 AND CHEMOSENSIT?

=> s l5 and multiple drug resistant
L6 15 L5 AND MULTIPLE DRUG RESISTANT

=> s l6 and cancer cell
L7 11 L6 AND CANCER CELL

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 11 DUP REM L7 (0 DUPLICATES REMOVED)

=> d l8 bib abs 1-11

L8 ANSWER 1 OF 11 USPATFULL on STN
AN 2003:201345 USPATFULL
TI **Treatment** of cancer by reduction of intracellular energy and pyrimidines
IN Martin, Daniel S., Pound Ridge, NY, UNITED STATES
Bertino, Joseph R., Branford, CT, UNITED STATES
Koutcher, Jason, New Rochelle, NY, UNITED STATES
PI US 2003139331 A1 20030724
AI US 2002-172346 A1 20020613 (10)
RLI Continuation-in-part of Ser. No. WO 2001-US46886, filed on 4 Dec 2001, PENDING
PRAI US 2000-250993P 20001204 (60)
DT Utility
FS APPLICATION
LREP Law Offices of Albert Wai-Kit Chan, LLC, World Plaza, Suite 604, 141-07 20th Avenue, Whitestone, NY, 11357
CLMN Number of Claims: 43
ECL Exemplary Claim: 1
DRWN 3 Drawing Page(s)
LN.CNT 4323
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for treating a cancer subject comprising administering to the subject a combination of ATP-depleting agents at concentrations which deplete the ATP level to at least 15% of normal in cancer cells, a pyrimidine antagonist, and an anticancer agent to which the treated cancer is **sensitive**. This invention also provides a composition comprising a combination of ATP-depleting agents at concentrations which deplete the ATP level to at least 15% of normal in cancer cells, a pyrimidine antagonist, and an anticancer agent to which the treated cancer is **sensitive**. Finally this invention provides a pharmaceutical composition comprising the above composition or a combination thereof and a pharmaceutically acceptable carrier.

09567863

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 2 OF 11 USPATFULL on STN
AN 2003:200449 USPATFULL
TI Selective cellular targeting: multifunctional delivery vehicles, multifunctional prodrugs, use as antineoplastic drugs
IN Glazier, Arnold, Newton, MA, UNITED STATES
PA Drug Innovation & Design, Inc. (U.S. corporation)
PI US 2003138432 A1 20030724
AI US 2000-738625 A1 20001215 (9)
RLI Continuation of Ser. No. US 2000-712465, filed on 15 Nov 2000, ABANDONED
PRAI US 1999-165485P 19991115 (60)
US 2000-239478P 20001011 (60)
US 2000-241939P 20001010 (60)
DT Utility
FS APPLICATION
LREP N. Scott Pierce, Esq., HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
CLMN Number of Claims: 29
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 18716
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the compositions, methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector molecules to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultra-low dose, multiple target, multiple drug **chemotherapy** and targeted immunotherapy for cancer **treatment**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 3 OF 11 USPATFULL on STN
AN 2003:120746 USPATFULL
TI Reversal of multidrug **resistance** in human colon carcinoma cells
IN Rabindran, Sridhar Krishna, Chestnut Ridge, NY, UNITED STATES
He, Haiyin, Washington Township, NJ, UNITED STATES
Greenberger, Lee Martin, Montclair, NJ, UNITED STATES
PA American Cyanamid Company, Madison, NJ (U.S. corporation)
PI US 2003083230 A1 20030501
AI US 2002-86133 A1 20020228 (10)
RLI Division of Ser. No. US 1999-321182, filed on 27 May 1999, GRANTED, Pat. No. US 6372775
PRAI US 1998-109801P 19980527 (60)
DT Utility
FS APPLICATION
LREP WYETH, FIVE GIRALDA FARMS, MADISON, NJ, 07940
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1811
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of fumitremorgin A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of **chemotherapeutic** drugs.

09567863

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 4 OF 11 USPATFULL on STN
AN 2003:81715 USPATFULL
TI Reversal of multidrug **resistance** in human colon carcinoma cells
IN He, Haiyin, Washington Township, NJ, United States
Greenberger, Lee Martin, Montclair, NJ, United States
PA Wyeth Holdings Corporation, United States (U.S. corporation)
PI US 6537964 B1 20030325
AI US 2002-86170 20020228 (10)
RLI Division of Ser. No. US 1999-321182, filed on 27 May 1999, now patented, Pat. No. US 6372775
PRAI US 1998-109801P 19980527 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Riley, Jezia
LREP Moran, Daniel B.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1424
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of fumitremorgin A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of **chemotherapeutic** drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 5 OF 11 USPATFULL on STN
AN 2002:301566 USPATFULL
TI Reversal of multidrug **resistance** in human colon carcinoma cells
IN He, Haiyin, Washington Township, NJ, UNITED STATES
Greenberger, Lee Martin, Montclair, NJ, UNITED STATES
PA American Cyanamid Comany, Madison, NJ, UNITED STATES, 07940-0874 (U.S. corporation)
PI US 2002169111 A1 20021114
AI US 2002-86132 A1 20020228 (10)
RLI Division of Ser. No. US 1999-321182, filed on 27 May 1999, GRANTED, Pat. No. US 6372775
PRAI US 1998-109801P 19980527 (60)
DT Utility
FS APPLICATION
LREP WYETH, FIVE GIRALDA FARMS, MADISON, NJ, 07940
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1794
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of fumitremorgin A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of **chemotherapeutic** drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 6 OF 11 USPATFULL on STN
AN 2002:287491 USPATFULL
TI METHODS FOR SCREENING THERAPEUTICALLY EFFECTIVE AGENTS

09567863

IN CABOT, MYLES C., SANTA MONICA, CA, UNITED STATES
PI US 2002160354 A1 20021031
AI US 1998-201115 A1 19981130 (9)
PRAI US 1997-67489P 19971201 (60)
DT Utility
FS APPLICATION
LREP MCCUTCHEN DOYLE BROWN & ENERSEN, THREE EMBARCADERO CENTER, SAN FRANCISCO, CA, 94111
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 18 Drawing Page(s)
LN.CNT 2166
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of detecting novel therapeutically active compositions based on their ability to modulate the glycolipid metabolism and overcome multidrug **resistance** are described. These methods are particularly useful in screening for novel **chemotherapeutic** agents for the **treatment** of cancer, as well as **chemosensitizers** that are capable of enhancing the cytotoxicity of such **chemotherapeutic** agents. A combination of one or more of these compositions can be used in the **treatment** of a various cancers.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 7 OF 11 USPATFULL on STN
AN 2002:280570 USPATFULL
TI Reversal of multidrug **resistance** in human colon carcinoma cells
IN Rabindran, Sridhar Krishna, Chestnut Ridge, NY, UNITED STATES
He, Haiyin, Washington Township, NJ, UNITED STATES
Singh, Maya Prakash, Bardonia, NY, UNITED STATES
Greenberger, Lee Martin, Montclair, NJ, UNITED STATES
PA American Cyanamid Company, Madison, NJ (U.S. corporation)
PI US 2002156015 A1 20021024
AI US 2002-86169 A1 20020228 (10)
RLI Division of Ser. No. US 1999-321182, filed on 27 May 1999, GRANTED, Pat. No. US 6372775
PRAI US 1998-109801P 19980527 (60)
DT Utility
FS APPLICATION
LREP WYETH, FIVE GIRALDA FARMS, MADISON, NJ, 07940
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1809
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of fumitremorgin A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of **chemotherapeutic** drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 8 OF 11 USPATFULL on STN
AN 2002:332761 USPATFULL
TI Fungal efflux pump inhibitors
IN Chamberland, Suzanne, Los Gatos, CA, United States
Lee, May, Los Altos, CA, United States
Lomovskaya, Olga, Mill Valley, CA, United States
PA Essential Therapeutics, Inc., Mountain View, CA, United States (U.S. corporation)

09567863

PI US 6495591 B1 20021217
AI US 1998-164609 19981001 (9)
PRAI US 1997-61322P 19971002 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Fay, Zohreh; Assistant Examiner: Delacroix-Muirheid, C.
LREP Bingham McCutchen, Rose, Bernard F.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 39 Drawing Figure(s); 36 Drawing Page(s)
LN.CNT 2027
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The use of compounds of the milbemycin class as inhibitors of efflux pumps in microbes or other cells is described, along with pharmaceutical compositions incorporating a milbemycin. Also described is a method of screening for compounds which inhibit a CDR1, CDR2, BEN, or FLU1 efflux pump or a pump with components having a high level of protein level sequence similarity with the components of those efflux pumps.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 9 OF 11 USPATFULL on STN
AN 2002:81514 USPATFULL
TI Reversal of multidrug **resistance** in human colon carcinoma cells
IN Rabindran, Sridhar Krishna, Chestnut Ridge, NY, United States
He, Haiyin, Washington Township, NJ, United States
Greenberger, Lee Martin, Montclair, NJ, United States
PA American Cyanamid Company, Madison, NJ, United States (U.S. corporation)
PI US 6372775 B1 20020416
AI US 1999-321182 19990527 (9)
PRAI US 1998-109801P 19980527 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Riley, Jezia
LREP Moran, Daniel B.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1478
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of fumitremorgin A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of **chemotherapeutic** drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 10 OF 11 USPATFULL on STN
AN 2000:150157 USPATFULL
TI Progesterone analogs to reverse multidrug **resistance**
IN Clarke, Robert, Rockville, MD, United States
Talebian, Abdel H., Herndon, VA, United States Gholan Talebian, Legal Representative
Ghiorghis, Alem, Silver Spring, MD, United States
Leonessa, Fabio, Takoma Park, MD, United States
Hammer, Charles, Santa Fe, NM, United States
PA Georgetown University, Washington, DC, United States (U.S. corporation)
PI US 6143737 20001107
AI US 1996-667542 19960621 (8)
PRAI US 1995-440P 19950623 (60)

09567863

DT Utility
FS Granted
EXNAM Primary Examiner: Dees, Jose' G.; Assistant Examiner: Badio, Barbara
LREP Sterne, Kessler, Goldstein & Fox P.L.L.C.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 1618
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to compounds of formula I ##STR1## wherein the substituents are as defined in the specification. Also disclosed are compositions and method of use of the compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 11 OF 11 USPATFULL on STN
AN 92:91010 USPATFULL
TI Tumor cell **sensitization** method using quinazolinedione derivatives
IN Klohs, Wayne, Ann Arbor, MI, United States
Ramu, Avner, Jerusalem, Israel
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
Hadasit Medical Research Services and Development, Jerusalem, Israel (non-U.S. corporation)
PI US 5160727 19921103
AI US 1990-497049 19900321 (7)
RLI Continuation-in-part of Ser. No. US 1990-479320, filed on 13 Feb 1990, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Goldberg, Jerome D.; Assistant Examiner: Criares, T. J.
LREP Newtson, Ruth H.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 416
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for **sensitizing** cancer cells which have become resistant to **treatment** with one or more anticancer agents which comprises treating said cells with a quinazolinedione compound.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=>

09567863

```
=> file biosis medline capls wpids uspatfull
'CAPLS' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    47.28      47.49

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -2.48      -2.48

FILE 'BIOSIS' ENTERED AT 09:52:14 ON 26 NOV 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'MEDLINE' ENTERED AT 09:52:14 ON 26 NOV 2003

FILE 'CAPLUS' ENTERED AT 09:52:14 ON 26 NOV 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIDS' ENTERED AT 09:52:14 ON 26 NOV 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE 'USPATFULL' ENTERED AT 09:52:14 ON 26 NOV 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

*** YOU HAVE NEW MAIL ***

=> s fumitremorgin? and chemosensit?
L3          22 FUMITREMORGIN? AND CHEMOSENSIT?

=> s l3 and multiple drug resistance
L4           7 L3 AND MULTIPLE DRUG RESISTANCE

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           5 DUP REM L4 (2 DUPLICATES REMOVED)

=> d l5 bib abs 1-5

L5   ANSWER 1 OF 5  USPATFULL on STN
AN     2003:120746  USPATFULL
TI     Reversal of multidrug resistance in human colon carcinoma cells
IN     Rabindran, Sridhar Krishna, Chestnut Ridge, NY, UNITED STATES
       He, Haiyin, Washington Township, NJ, UNITED STATES
       Greenberger, Lee Martin, Montclair, NJ, UNITED STATES
PA     American Cyanamid Company, Madison, NJ (U.S. corporation)
PI     US 2003083230      A1   20030501
AI     US 2002-86133      A1   20020228 (10)
RLI    Division of Ser. No. US 1999-321182, filed on 27 May 1999, GRANTED, Pat.
       No. US 6372775
PRAI   US 1998-109801P     19980527 (60)
DT     Utility
FS     APPLICATION
LREP   WYETH, FIVE GIRALDA FARMS, MADISON, NJ, 07940
CLMN   Number of Claims: 63
```

09567863

ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1811
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of **fumitremorgin** A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of chemotherapeutic drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 2 OF 5 USPATFULL on STN
AN 2003:81715 USPATFULL
TI Reversal of multidrug resistance in human colon carcinoma cells
IN He, Haiyin, Washington Township, NJ, United States
Greenberger, Lee Martin, Montclair, NJ, United States
PA Wyeth Holdings Corporation, United States (U.S. corporation)
PI US 6537964 B1 20030325
AI US 2002-86170 20020228 (10)
RLI Division of Ser. No. US 1999-321182, filed on 27 May 1999, now patented, Pat. No. US 6372775
PRAI US 1998-109801P 19980527 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Riley, Jezia
LREP Moran, Daniel B.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1424
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of **fumitremorgin** A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of chemotherapeutic drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 3 OF 5 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 1
AN 2003-605671 [57] WPIDS
CR 2002-424735 [45]; 2003-491922 [46]
DNC C2003-164793
TI Identification of **chemosensitizing** compounds that reverse non P-glycoprotein/non **multiple drug resistance** protein **multiple drug resistance** in cancer cells by administering test compound and chemotherapeutic agent.
DC B02 B04 D16
IN GREENBERGER, L M; HE, H
PA (AMCY) AMERICAN CYANAMID CO
CYC 1
PI US 2002169111 A1 20021114 (200357)* 27p
ADT US 2002169111 A1 Provisional US 1998-109801P 19980527, Div ex US 1999-321182 19990527, US 2002-86132 20020228
FDT US 2002169111 A1 Div ex US 6372775
PRAI US 1998-109801P 19980527; US 1999-321182 19990527; US 2002-86132 20020228
AN 2003-605671 [57] WPIDS
CR 2002-424735 [45]; 2003-491922 [46]
AB US2002169111 A UPAB: 20030906
NOVELTY - Method of identifying **chemosensitizing** compounds that reverse non P-glycoprotein (P-gp)/non **multiple drug resistance** protein (MRP) **multiple drug**

resistance in cancer cells exhibiting non P-gp/non MRP drug resistance phenotype involves:

(i) administering a test compound and a chemotherapeutic agent to which cancer cells are resistant; and

(ii) measuring cancer cell survival.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) resensitizing/distinguishing breast cancer resistance protein (BCRP)-mediated multiple drug resistant cancer cells to treatment with chemotherapeutic agents to which cancer cells have developed resistance comprising administration of a **chemosensitizing** reversal agent and a chemotherapeutic agent;

(2) determining the presence and magnitude of cancer cell BCRP or other non P-gp/non MRP resistance in cancer cells exhibiting the resistance, comprising administration of a **chemosensitizing** reversal agent and chemotherapeutic agents to resistant cancer cells from humans and measuring cancer cell survival;

(3) inhibiting efflux of a chemotherapeutic agent in a mammal comprising administering a **chemosensitizing** reversal agent and a chemotherapeutic agent to which the cancer is resistant;

(4) a compound of formula (I) or its pharmaceutically acceptable salt;

(5) a pharmaceutical composition for resensitizing multiple drug resistant chemotherapeutic agents comprising the compound of formula (I);

(6) treating **multiple drug resistance** in a mammal, by administering to the mammal, a chemotherapeutic agent and a **chemosensitizing** reversal agent of formula (I) or its pharmaceutically acceptable salt;and

(7) a culture of the organism Aspergillus fumigatus having the identifying characteristics of LL-S266. The culture produces **Fumitremorgin** A, B and C in recoverable quantity upon fermentation in an aqueous nutrient medium containing assimilable sources of carbon and nitrogen.

n = 0, 1, or 2;

R1 = hydrogen or 1-10C alkoxy;

R2 = H or 2-10C alkenyl;

R3 = H, 1-10 alkyl, 2-10C alkenyl, R7-NH(CH2)v-, or (CH2)m-phenyl;

m = 1-6;

v = 1-4;

R4-R6 = H;

R7 = H or COR8;

R8 = 1-10C alkyl, -(CH2)mCO2H, OCH2-phenyl or (CH2)m-(2-pyrrolidinyl); and

provided that n is not 1, when:

(a) R1 is hydrogen or -OCH3;

(b) R2 is H, -CH2CH2CH(CH3)2, -CH2CH(CH3)2 or -CH=C(CH3)2; and

(c) R4-R5 are hydrogen.

ACTIVITY - Cytostatic.

The reversal activity of **Fumitremorgin** C (FTC) in BRCP-transfected cells was determined using a fixed dose of FTC in combination with increasing doses of antitumor drugs Mitoxantrone, Doxorubicin, Topotecan and Paclitaxel. Cell survival was estimated after 3 days and EC50 values were determined from cytotoxicity curves. FTC (5 micro M) potentiated the toxicity of mitoxantrone (29.4-fold), doxorubicin (6.6-fold) and topotecan (6.5-fold). No reversal activity was detected with paclitaxel (1.1-fold). The IC50 of FTC was 0.3.

MECHANISM OF ACTION - Potent P-gp Inhibitor.

USE - For identifying **chemosensitizing** compounds that reverse non P-gp/non MRP **multiple drug resistance** in cancer cells exhibiting non P-gp/non MRP drug resistance phenotype.

ADVANTAGE - The invention is capable of identifying test compounds as **chemosensitizing** agents following evaluation in an assay.

09567863

Dwg.0/0

L5 ANSWER 4 OF 5 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 2
AN 2003-491922 [46] WPIDS
CR 2002-424735 [45]; 2003-605671 [57]
DNC C2003-131458
TI Identifying **chemosensitizing** compounds that reverse non P-glycoprotein/non **multiple drug resistance** protein in cancer cells comprises administering test compound and chemotherapeutic agent and measuring cancer cell survival.
DC B04 B05
IN GREENBERGER, L M; HE, H; RABINDRAN, S K; SINGH, M P
PA (AMCY) AMERICAN CYANAMID CO
CYC 1
PI US 2002156015 A1 20021024 (200346)* 28p
ADT US 2002156015 A1 Provisional US 1998-109801P 19980527, Div ex US 1999-321182 19990527, US 2002-86169 20020228
FDT US 2002156015 A1 Div ex US 6372775
PRAI US 1998-85549 19980527; US 1998-109801P 19980527; US 1999-321182 19990527; US 2002-86169 20020228
AN 2003-491922 [46] WPIDS
CR 2002-424735 [45]; 2003-605671 [57]
AB US2002156015 A UPAB: 20030906
NOVELTY - Identifying **chemosensitizing** compounds that reverse non P-glycoprotein (P-gp)/non **multiple drug resistance** protein (MRP) in cancer cells exhibiting non P-gp/non MRP phenotype, or reverse breast cancer resistant protein (BCRP)-mediated **multiple drug resistance** in cancer cells comprises administering a test compound and a chemotherapeutic agent to which cancer cells are resistant and measuring cancer cell survival.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) resensitizing non P-gp/non MRP, or BCRP-mediated multiple drug resistant cancer cells to treatment with chemotherapeutic agents to which cancer cells have developed resistance, which comprises administering a **chemosensitizing** reversal agent (I) and a chemotherapeutic agent;

(2) distinguishing (M3) P-gp/MRP resistance from BCRP or other non P-gp/non MRP resistance which comprises administering (I) and a chemotherapeutic agent and measuring cancer cell survival or accumulations of chemotherapeutic agent in the cell;

(3) determining the presence and magnitude of cancer cell BCRP or other non P-gp/non MRP resistance in cancer cells which comprises administering (I) and a chemotherapeutic agent to resistant cancer cells from humans and measuring cancer cell survival;

(4) new pyridopyrazinopyridoindoledione compounds of formula (I') and their salts, and

(5) a culture of the organism Aspergillus fumigatus having the identifying characteristics of LL-S266. The culture is capable of producing **fumitremorgin** A, B, and C in recoverable quantity upon fermentation in an aqueous nutrient medium containing assimilable sources of carbon and nitrogen.

n = 0-2;
R1 = H or 1-10C alkoxy;
R2 = H or 2-10C alkenyl;
R3 = H, 1-10C alkyl, 2-10C alkenyl, R7NH(CH2)v- or a group of formula (i);
m = 1-6;
v = 1-4;
R4-R6 = H;
R7 = H or CO-R8;
R8 = 1-10C alkyl, (CH2)mCO2H, benzyloxy or a group of formula (ii), provided that n is not 1 when R1 = H or CH3O and R2 = H or

CH2CH2CH(Me)2, CH2CH(Me)2 or CH=C(Me)2.

ACTIVITY - Cytostatic.

In a test for resensitizing the S1-M1-3.2 human colon cancer cells to mitoxantrone, (5aS,12R,14aS)-12-nonyl-1,2,3,5a,6,11,12,14a-octahydro-5H,14H-pyrrolo(1'',2'':4',5')pyrazino(2',1':6,1)pyrido(3,4-b)indole-5,14-dione (I'a) exhibited an IC50 value of 0.25 mu M.

MECHANISM OF ACTION - None given in the source material.

USE - Used for reversing BCRP or other non P-gp/non MRP resistance to chemotherapeutic agents, for identifying **chemosensitizing** compounds that reverse non P-glycoprotein (P-gp)/non MRP, or BCRP-mediated **multiple drug resistance** in cancer cells exhibiting non P-gp/non MRP phenotype, or BCRP-mediated **multiple drug resistance**, resensitizing non P-gp/non MRP, or BCRP-mediated multiple drug resistant cancer cells for treatment with chemotherapeutic agents to which cancer cells have developed resistance, for distinguishing P-gp/MRP resistance from BCRP or other non P-gp/non MRP resistance, and determining the presence and magnitude of cancer cell BCRP or other non P-gp/non MRP resistance in cancer cells.

Dwg.0/0

L5 ANSWER 5 OF 5 USPATFULL on STN
AN 2002:81514 USPATFULL
TI Reversal of multidrug resistance in human colon carcinoma cells
IN Rabindran, Sridhar Krishna, Chestnut Ridge, NY, United States
He, Haiyin, Washington Township, NJ, United States
Greenberger, Lee Martin, Montclair, NJ, United States
PA American Cyanamid Company, Madison, NJ, United States (U.S. corporation)
PI US 6372775 B1 20020416
AI US 1999-321182 19990527 (9)
PRAI US 1998-109801P 19980527 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Riley, Jezia
LREP Moran, Daniel B.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1478
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of **fumitremorgin** A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of chemotherapeutic drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d his

(FILE 'HOME' ENTERED AT 09:35:43 ON 26 NOV 2003)

FILE 'REGISTRY' ENTERED AT 09:35:53 ON 26 NOV 2003
E FUMITREMORGIN/CN
L1 2 S E6
E SPIROTRYPROSTATINS/CN
L2 2 S E1-E2

FILE 'BIOSIS, MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 09:52:14 ON 26 NOV 2003
L3 22 S FUMITREMORGIN? AND CHEMOSENSIT?
L4 7 S L3 AND MULTIPLE DRUG RESISTANCE
L5 5 DUP REM L4 (2 DUPLICATES REMOVED)

09567863

```
=> s l3 not l5
L6          17 L3 NOT L5

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7            8 DUP REM L6 (9 DUPLICATES REMOVED)

=> d l7 bib abs 1-8

L7   ANSWER 1 OF 8  USPATFULL on STN
AN     2003:200449  USPATFULL
TI     Selective cellular targeting: multifunctional delivery vehicles,
       multifunctional prodrugs, use as antineoplastic drugs
IN     Glazier, Arnold, Newton, MA, UNITED STATES
PA     Drug Innovation & Design, Inc. (U.S. corporation)
PI     US 2003138432      A1   20030724
AI     US 2000-738625     A1   20001215 (9)
RLI    Continuation of Ser. No. US 2000-712465, filed on 15 Nov 2000, ABANDONED
PRAI   US 1999-165485P     19991115 (60)
       US 2000-239478P     20001011 (60)
       US 2000-241939P     20001010 (60)
DT     Utility
FS     APPLICATION
LREP   N. Scott Pierce, Esq., HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two
       Militia Drive, Lexington, MA, 02421-4799
CLMN   Number of Claims: 29
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 18716
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     The present invention relates to the compositions, methods, and
       applications of a novel approach to selective cellular targeting. The
       purpose of this invention is to enable the selective delivery and/or
       selective activation of effector molecules to target cells for
       diagnostic or therapeutic purposes. The present invention relates to
       multi-functional prodrugs or targeting vehicles wherein each
       functionality is capable of enhancing targeting selectivity, affinity,
       intracellular transport, activation or detoxification. The present
       invention also relates to ultra-low dose, multiple target, multiple drug
       chemotherapy and targeted immunotherapy for cancer treatment.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7   ANSWER 2 OF 8  USPATFULL on STN
AN     2002:301566  USPATFULL
TI     Reversal of multidrug resistance in human colon carcinoma cells
IN     He, Haiyin, Washington Township, NJ, UNITED STATES
       Greenberger, Lee Martin, Montclair, NJ, UNITED STATES
PA     American Cyanamid Comany, Madison, NJ, UNITED STATES, 07940-0874 (U.S.
       corporation)
PI     US 2002169111      A1   20021114
AI     US 2002-86132      A1   20020228 (10)
RLI    Division of Ser. No. US 1999-321182, filed on 27 May 1999, GRANTED, Pat.
       No. US 6372775
PRAI   US 1998-109801P     19980527 (60)
DT     Utility
FS     APPLICATION
LREP   WYETH, FIVE GIRALDA FARMS, MADISON, NJ, 07940
CLMN   Number of Claims: 63
ECL    Exemplary Claim: 1
DRWN   No Drawings
```

09567863

LN.CNT 1794
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of **fumitremorgin** A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of chemotherapeutic drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 8 USPATFULL on STN
AN 2002:280570 USPATFULL
TI Reversal of multidrug resistance in human colon carcinoma cells
IN Rabindran, Sridhar Krishna, Chestnut Ridge, NY, UNITED STATES
He, Haiyin, Washington Township, NJ, UNITED STATES
Singh, Maya Prakash, Bardonia, NY, UNITED STATES
Greenberger, Lee Martin, Montclair, NJ, UNITED STATES
PA American Cyanamid Company, Madison, NJ (U.S. corporation)
PI US 2002156015 A1 20021024
AI US 2002-86169 A1 20020228 (10)
RLI Division of Ser. No. US 1999-321182, filed on 27 May 1999, GRANTED, Pat. No. US 6372775
PRAI US 1998-109801P 19980527 (60)
DT Utility
FS APPLICATION
LREP WYETH, FIVE GIRALDA FARMS, MADISON, NJ, 07940
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1809
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention describes the use of **fumitremorgin** A, B and C and a series of diketopiperazines of Formula (I) to resensitize multidrug resistant (MDR) cancer cells to the cytotoxic effects of chemotherapeutic drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1
AN 2002:306853 BIOSIS
DN PREV200200306853
TI Potent and specific inhibition of the breast cancer resistance protein multidrug transporter in vitro and in mouse intestine by a novel analogue of **fumitremorgin** C.
AU Allen, John D.; van Loevezijn, Arnold; Lakhai, Jeany M.; van der Valk, Martin; Van Tellingen, Olaf; Reid, Glen; Schellens, Jan H. M.; Koomen, Gerrit-Jan; Schinkel, Alfred H. [Reprint author]
CS Division of Experimental Therapy, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, Netherlands
a.schinkel@nki.nl
SO Molecular Cancer Therapeutics, (April, 2002) Vol. 1, No. 6, pp. 417-425. print.
ISSN: 1535-7163.
DT Article
LA English
ED Entered STN: 22 May 2002
Last Updated on STN: 22 May 2002
AB Inhibitors of the breast cancer resistance protein (BCRP/ABCG2) multidrug transporter are of interest as **chemosensitizers** for clinical drug resistance, for improving the pharmacokinetics of substrate chemotherapeutic drugs, and in functional assays of BCRP activity for tailoring chemotherapy. The fungal toxin **fumitremorgin** C (FTC)

is a potent and specific inhibitor of BCRP, but its neurotoxic effects preclude use in vivo. We have therefore evaluated a new tetracyclic analogue of FTC, Ko143, as a practical inhibitor of BCRP, comparing it with two other analogues in the same class and with GF120918. All three FTC analogues are effective inhibitors of both mouse Bcrp1 and human BCRP, proving highly active for increasing the intracellular drug accumulation and reversing Bcrp1/BCRP-mediated multidrug resistance. Indeed, Ko143 appears to be the most potent BCRP inhibitor known thus far. In contrast, the compounds have only low activity against P-glycoprotein, the multidrug resistance-associated protein (MRP1), or other known drug transporters. They are nontoxic in vitro at useful concentrations and evinced no signs of toxicity in mice at high oral or i.p. doses. Administered p.o. to inhibit intestinal Bcrp1, Ko143 markedly increased the oral availability of topotecan in mice. It is thus the first highly potent and specific BCRP inhibitor applicable in vivo. As such, Ko143 and other FTC analogues of this type represent valuable reagents for analysis of drug resistance mechanisms and may be candidates for development as clinical BCRP inhibitors.

L7 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2
AN 2000:110068 BIOSIS
DN PREV200000110068
TI **Fumitremorgin** C reverses multidrug resistance in cells transfected with the breast cancer resistance protein.
AU Rabindran, Sridhar K. [Reprint author]; Ross, Douglas D.; Doyle, L. Austin; Yang, Weidong; Greenberger, Lee M.
CS Wyeth-Ayerst Research, 401 North Middletown Road, Building 200, Room 4608, Pearl River, NY, 10965, USA
SO Cancer Research, (Jan., 2000) Vol. 60, No. 1, pp. 47-50. print.
CODEN: CNREA8. ISSN: 0008-5472.
DT Article
LA English
ED Entered STN: 22 Mar 2000
Last Updated on STN: 3 Jan 2002
AB **Fumitremorgin** C (FTC) is a potent and specific **chemosensitizing** agent in cell lines selected for resistance to mitoxantrone that do not overexpress P-glycoprotein or multidrug resistance protein. The gene encoding a novel transporter, the breast cancer resistance protein (BCRP), was recently found to be overexpressed in a mitoxantrone-selected human colon cell line, S1-M1-3.2, which was used to identify FTC. Because the drug-selected cell line may contain multiple alterations contributing to the multidrug resistance phenotype, we examined the effect of FTC on MCF-7 cells transfected with the BCRP gene. We report that FTC almost completely reverses resistance mediated by BCRP in vitro and is a pharmacological probe for the expression and molecular action of this transporter.

L7 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3
AN 1999:166654 BIOSIS
DN PREV199900166654
TI Multiple mechanisms confer drug resistance to mitoxantrone in the human 8226 myeloma cell line.
AU Hazlehurst, Lori A.; Foley, Nils E.; Gleason-Guzman, Mary C.; Hacker, Miles P.; Cress, Anne E.; Greenberger, Lee W.; De Jong, Mariska C.; Dalton, William S. [Reprint author]
CS H. Lee Moffitt Cancer Center Res. Inst., 12902 Magnolia Drive, Tampa, FL 33612-9497, USA
SO Cancer Research, (March 1, 1999) Vol. 59, No. 5, pp. 1021-1028. print.
CODEN: CNREA8. ISSN: 0008-5472.
DT Article

09567863

LA English
ED Entered STN: 19 Apr 1999
Last Updated on STN: 19 Apr 1999
AB Selection for in vitro drug resistance can result in a complex phenotype with more than one mechanism of resistance emerging concurrently or sequentially. We examined emerging mechanisms of drug resistance during selection with mitoxantrone in the human myeloma cell line 8226. A novel transport mechanism appeared early in the selection process that was associated with a 10-fold resistance to mitoxantrone in the 8226/MR4 cell line. The reduction in intracellular drug concentration was ATP-dependent and ouabain-insensitive. The 8226/MR4 cell line was 34-fold cross-resistant to the fluorescent aza-anthrapyrazole BBR 3390. The resistance to BBR 3390 coincided with a 50% reduction in intracellular drug concentration. Confocal microscopy using BBR 3390 revealed a 64% decrease in the nuclear:cytoplasmic ratio in the drug-resistant cell line. The reduction in intracellular drug concentration of both mitoxantrone and BBR 3390 was reversed by a novel **chemosensitizing** agent, **fumitremorgin** C. In contrast, **fumitremorgin** C had no effect on resistance to mitoxantrone or BBR 3390 in the P-glycoprotein-positive 8226/DOX6 cell line. Increasing the degree of resistance to mitoxantrone in the 8226 cell line from 10 to 37 times (8226/MR20) did not further reduce the intracellular drug concentration. However, the 8226/MR20 cell line exhibited 88 and 70% reductions in topoisomerase II beta and alpha expression, respectively, compared with the parental drug sensitive cell line. This decrease in topoisomerase expression and activity was not observed in the low-level drug-resistant, 8226/MR4 cell line. These data demonstrate that low-level mitoxantrone resistance is due to the presence of a novel, energy-dependent drug efflux pump similar to P-glycoprotein and multidrug resistance-associated protein. Reversal of resistance by blocking drug efflux with **fumitremorgin** C should allow for functional analysis of this novel transporter in cancer cell lines or clinical tumor samples. Increased resistance to mitoxantrone may result from reduced intracellular drug accumulation, altered nuclear/cytoplasmic drug distribution, and alterations in topoisomerase II activity.

L7 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 4
AN 2000:92915 BIOSIS
DN PREV200000092915
TI **Fumitremorgin** C analogs that reverse mitoxantrone resistance in human colon carcinoma cells.
AU He, Haiyin [Reprint author]; Rabindran, Sridhar G.; Greenberger, Lee M.; Carter, Guy T.
CS Natural Products Chemistry, Wyeth-Ayerst Research, 401 Middletown Road, Pearl River, NY, 10965, USA
SO Medicinal Chemistry Research, (1999) Vol. 9, No. 6, pp. 424-437. print. ISSN: 1054-2523.
DT Article
LA English
ED Entered STN: 10 Mar 2000
Last Updated on STN: 3 Jan 2002
AB A series of diketopiperazines (1a) that mimic the natural product, **fumitremorgin** C (1), were synthesized. This class of compounds enhanced the sensitivity of a mitoxantrone-selected colon carcinoma cell line, S1-M1-3.2, to various antitumor agents, thereby reversing multidrug resistance. An SAR study showed that the presence of a lipid chain at C-x in the S configuration is essential for retaining strong **chemosensitizing** activity.

L7 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 5

09567863

AN 1999:46846 BIOSIS
DN PREV199900046846
TI Reversal of a novel multidrug resistance mechanism in human colon carcinoma cells by **fumitremorgin** C.
AU Rabindran, Sridhar K. [Reprint author]; He, Haiyin; Singh, Maya; Brown, Eileen; Collins, Karen I.; Annable, Tami; Greenberger, Lee M.
CS Wyeth-Ayerst Res., Build. 200, Room 4608, 401 North Middletown Rd., Pearl River, NY 10965, USA
SO Cancer Research, (Dec. 15, 1998) Vol. 58, No. 24, pp. 5850-5858. print. CODEN: CNREA8. ISSN: 0008-5472.
DT Article
LA English
ED Entered STN: 10 Feb 1999
Last Updated on STN: 10 Feb 1999
AB We selected a human colon carcinoma cell line in increasing concentrations of mitoxantrone to obtain a resistant subline, S1-M1-3.2, with the following characteristics: profound resistance to mitoxantrone; significant cross-resistance to doxorubicin, bisantrene, and topotecan; and very low levels of resistance to Taxol, vinblastine, colchicine, and camptothecin. This multidrug resistance (MDR) phenotype, which was not reversed by verapamil or another potent P-glycoprotein (Pgp) inhibitor, CL 329,753, was dependent, in part, upon an energy-dependent drug efflux mechanism. Pgp and the multidrug resistance protein (MRP) were not elevated in the resistant cells relative to the drug-sensitive parent, suggesting that resistance was mediated by a novel pathway of drug transport. A cell-based screen with S1-M1-3.2 cells was used to identify agents capable of circumventing this non-Pgp, non-MRP MDR. One of the active agents identified was a mycotoxin, **fumitremorgin** C. This molecule was extremely effective in reversing resistance to mitoxantrone, doxorubicin, type. Reversal of resistance was associated with an increase in drug accumulation. The compound did not reverse drug resistance in cells with elevated expression of Pgp or MRP. We suggest that **fumitremorgin** C is a highly selective **chemosensitizing** agent for the resistance pathway we have identified and can be used as a specific pharmacological probe to distinguish between the diverse resistance mechanisms that occur in the MDR cell.

=>